ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Delstrigo 100 mg/300 mg/245 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 100 mg of doravirine, 300 mg of lamivudine (3TC), and 245 mg of tenofovir disoproxil as tenofovir disoproxil fumarate (TDF).

Excipient with known effect

Each film-coated tablet contains 8.6 mg lactose (as monohydrate).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet (tablet).

Yellow, oval-shaped, tablet of dimensions 21.59 mm x 11.30 mm, debossed with the corporate logo and 776 on one side and plain on the other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Delstrigo is indicated for the treatment of adults infected with human immunodeficiency virus type 1 (HIV-1) without past or present evidence of resistance to the non-nucleoside reverse transcriptase inhibitors (NNRTI) class, lamivudine, or tenofovir (see sections 4.4 and 5.1).

Delstrigo is also indicated for the treatment of adolescents aged 12 years and older weighing at least 35 kg who are infected with HIV-1 without past or present evidence of resistance to the NNRTI class, lamivudine, or tenofovir and who have experienced toxicities which preclude the use of other regimens that do not contain tenofovir disoproxil (see sections 4.4 and 5.1).

4.2 Posology and method of administration

Therapy should be initiated by a physician experienced in the management of HIV infection.

Posology

The recommended dose of Delstrigo is one 100/300/245 mg tablet taken orally once daily with or without food.

Dose adjustment
If Delstrigo is co-administered with rifabutin, the doravirine dose should be increased to 100 mg twice daily. This is achieved by adding one 100 mg tablet of doravirine (as a single agent), to be taken approximately 12 hours apart from the dose of Delstrigo (see section 4.5).

Co-administration of doravirine with other moderate CYP3A inducers has not been evaluated, but decreased doravirine concentrations are expected. If co-administration with other moderate CYP3A inducers (e.g., dabrafenib, lesinurad, bosentan, thioridazine, nafcillin, modafinil, telotristat ethyl) cannot be avoided, one 100 mg tablet of doravirine should be taken daily, approximately 12 hours after the dose of Delstrigo (see section 4.5).

Missed dose
If the patient misses a dose of Delstrigo within 12 hours of the time it is usually taken, the patient should take Delstrigo as soon as possible and resume the normal dosing schedule. If a patient misses a dose of Delstrigo by more than 12 hours, the patient should not take the missed dose and instead take the next dose at the regularly scheduled time. The patient should not take 2 doses at one time.

Special populations

Elderly
There are limited data available on the use of doravirine, lamivudine, and tenofovir disoproxil in patients aged 65 years and over. There is no evidence that elderly patients require a different dose than younger adult patients (see section 5.2). Special care is advised in this age group due to age associated changes such as decreases in renal function (see section 4.4).

Renal impairment
No dose adjustment of Delstrigo is required in patients with estimated creatinine clearance (CrCl) ≥ 50 mL/min.

Delstrigo should not be initiated in patients with estimated CrCl < 50 mL/min (see sections 4.4 and 5.2). Delstrigo should be discontinued if estimated CrCl declines below 50 mL/min (see section 4.4). Patients with moderate or severe renal impairment require a dose interval adjustment of lamivudine and tenofovir disoproxil that cannot be achieved with the combination tablet (see sections 4.4 and 5.2).

Hepatic impairment
No dose adjustment of doravirine/lamivudine/tenofovir disoproxil is required in patients with mild (Child-Pugh Class A) or moderate (Child-Pugh Class B) hepatic impairment. Doravirine has not been studied in patients with severe hepatic impairment (Child-Pugh Class C). It is not known whether the exposure to doravirine will increase in patients with severe hepatic impairment. Therefore, caution is advised when doravirine/lamivudine/tenofovir disoproxil is administered to patients with severe hepatic impairment (see section 5.2).

Paediatric population
Safety and efficacy of Delstrigo in children aged less than 12 years or weighing less than 35 kg have not been established. No data are available.

Method of administration

Delstrigo must be taken orally, once daily with or without food and swallowed whole (see section 5.2).

4.3 Contraindications

Hypersensitivity to the active substances or to any of the excipients listed in section 6.1.

Co-administration with medicinal products that are strong cytochrome P450 CYP3A enzyme inducers is contraindicated as significant decreases in doravirine plasma concentrations are expected to occur, which may decrease the effectiveness of Delstrigo (see sections 4.4 and 4.5). These medicinal products include, but are not limited to the following:

- carbamazepine, oxcarbazepine, phenobarbital, phenytoin
- rifampicin, rifapentine
- St. John's wort (*Hypericum perforatum*)
- mitotane
- enzalutamide
- lumacaftor

4.4 Special warnings and precautions for use

NNRTI substitutions and use of doravirine

Doravirine has not been evaluated in patients with previous virologic failure to any other antiretroviral therapy. NNRTI-associated mutations detected at screening were part of exclusion criteria in the Phase 2b/3-studies. A breakpoint for a reduction in susceptibility, yielded by various NNRTI substitutions, that is associated with a reduction in clinical efficacy has not been established (see section 5.1). There is not sufficient clinical evidence to support the use of doravirine in patients infected with HIV-1 with evidence of resistance to the NNRTI class.

Severe cutaneous adverse reactions (SCARs)

Severe cutaneous adverse reactions (SCARs), including Stevens-Johnson syndrome (SJS)/toxic epidermal necrolysis (TEN), have been reported during the post-marketing experience with doravirine-containing regimens (see section 4.8). At the time of prescription, patients should be advised of the signs and symptoms and monitored closely for skin reactions. If signs and symptoms suggestive of these reactions appear, doravirine-containing regimens should be withdrawn immediately and an alternative treatment considered (as appropriate). Clinical status should be closely monitored, and appropriate therapy should be initiated. If the patient has developed a serious reaction such as TEN, with the use of doravirine-containing regimens, treatment with doravirine-containing regimens must not be restarted in this patient at any time.

Severe acute exacerbation of hepatitis B in patients co-infected with HIV-1 and HBV

All patients with HIV-1 should be tested for the presence of hepatitis B virus (HBV) before initiating antiretroviral therapy.

Severe acute exacerbations of hepatitis B (e.g., liver decompensated and liver failure) have been reported in patients who are co-infected with HIV-1 and HBV, and have discontinued lamivudine or tenofovir disoproxil, two of the components of Delstrigo. Patients who are co-infected with HIV-1 and HBV should be closely monitored with both clinical and laboratory follow-up for at least several months after stopping treatment with Delstrigo. If appropriate, initiation of anti-hepatitis B therapy may be warranted, especially in patients with advanced liver disease or cirrhosis, since post-treatment exacerbation of hepatitis may lead to hepatic decompensation and liver failure.

New onset or worsening renal impairment

Renal impairment, including cases of acute renal failure and Fanconi syndrome (renal tubular injury with severe hypophosphataemia), has been reported with the use of tenofovir disoproxil, a component of Delstrigo.

Delstrigo should be avoided with concurrent or recent use of nephrotoxic medicinal products (e.g., high-dose or multiple nonsteroidal anti-inflammatory medicinal products [NSAIDs]) (see section 4.5). Cases of acute renal failure after initiation of high-dose or multiple NSAIDs have been reported in HIV-infected patients with risk factors for renal dysfunction who appeared stable on tenofovir disoproxil. Some patients required hospitalisation and renal replacement therapy. Alternatives to NSAIDs should be considered, if needed, in patients at risk for renal dysfunction.

Persistent or worsening bone pain, pain in extremities, fractures, and/or muscular pain or weakness may be manifestations of proximal renal tubulopathy and should prompt an evaluation of renal function in at risk patients.

It is recommended that estimated CrCl be assessed in all patients prior to initiating therapy and as clinically appropriate during therapy with Delstrigo. In patients at risk of renal dysfunction, including patients who have previously experienced renal events while receiving adefovir dipivoxil, it is recommended that estimated CrCl, serum phosphorus, urine glucose, and urine protein be assessed

prior to initiation of Delstrigo and more frequent renal function monitoring should be assessed as appropriate per the patient's medical condition during Delstrigo therapy.

Lamivudine and tenofovir disoproxil are primarily excreted by the kidney. Delstrigo should be discontinued if estimated CrCl declines below 50 mL/min as dose interval adjustment required for lamivudine and tenofovir disoproxil cannot be achieved with the fixed dose combination tablet (see section 4.2).

Bone effects in adult population

Bone abnormalities such as osteomalacia which can manifest as persistent or worsening bone pain and, which can infrequently contribute to fractures may be associated with tenofovir disoproxil induced proximal renal tubulopathy (see section 4.8).

Reductions of bone mineral density (BMD) have been observed with tenofovir disoproxil in randomised controlled clinical trials of duration up to 144 weeks in HIV or HBV-infected patients. These BMD decreases generally improved after treatment discontinuation.

In other studies (prospective and cross-sectional), the most pronounced decreases in BMD were seen in patients treated with tenofovir disoproxil as part of a regimen containing a boosted protease inhibitor.

Overall, in view of the bone abnormalities associated with tenofovir disoproxil and the limitations of long-term data on the impact of tenofovir disoproxil on bone health and fracture risk, alternative treatment regimens should be considered for patients with osteoporosis or with a history of bone fractures.

If bone abnormalities are suspected or detected, then appropriate consultation should be obtained.

Bone effects in paediatric population

There are uncertainties associated with the long-term effects of bone toxicity. Therefore, a multidisciplinary approach is recommended to adequately weigh on a case-by-case basis the benefit/risk balance of treatment, decide the appropriate monitoring during treatment (including decision for treatment withdrawal) and consider the need for supplementation.

Tenofovir disoproxil may cause a reduction in BMD. The effects of tenofovir disoproxil-associated changes in BMD on long-term bone health and future fracture risk are uncertain.

If bone abnormalities are detected or suspected in paediatric patients, consultation with an endocrinologist and/or nephrologist should be obtained.

Co-administration with other antiviral products

Doravirine/lamivudine/tenofovir disoproxil must not be co-administered with other medicinal products containing lamivudine, or with medicinal products containing tenofovir disoproxil, or tenofovir alafenamide, or with adefovir dipivoxil (see section 4.5). Doravirine/lamivudine/tenofovir disoproxil should not be administered with doravirine unless needed for dose adjustment (e.g., with rifabutin) (see sections 4.2 and 4.5).

Use with CYP3A inducers

Caution should be given to prescribing doravirine with medicinal products that may reduce the exposure of doravirine (see sections 4.3 and 4.5).

Immune reactivation syndrome

Immune reactivation syndrome has been reported in patients treated with combination antiretroviral therapy. During the initial phase of combination antiretroviral treatment, patients whose immune system responds may develop an inflammatory response to indolent or residual opportunistic infections (such as *Mycobacterium avium* infection, cytomegalovirus, *Pneumocystis jirovecii* pneumonia [PCP], or tuberculosis), which may necessitate further evaluation and treatment.

Autoimmune disorders (such as Graves' disease, autoimmune hepatitis, polymyositis, and Guillain-Barré syndrome) have also been reported to occur in the setting of immune reactivation; however, the time to onset is more variable and can occur many months after initiation of treatment.

Lactose

Delstrigo contains lactose monohydrate. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

4.5 Interaction with other medicinal products and other forms of interaction

Delstrigo is a complete regimen for the treatment of HIV-1 infection; therefore, Delstrigo should not be administered with other antiretroviral medicinal products. Information regarding potential medicinal product interactions with other antiretroviral medicinal products is not provided.

Interaction studies have only been performed in adults.

Delstrigo contains doravirine, lamivudine, and tenofovir disoproxil, therefore any interactions identified for these individually are relevant to Delstrigo and are presented in Table 1.

Effects of other medicinal products on doravirine, lamivudine, and tenofovir disoproxil

Doravirine
Doravirine is primarily metabolised by CYP3A, and medicinal products that induce or inhibit CYP3A are expected to affect the clearance of doravirine (see section 5.2). Doravirine/lamivudine/tenofovir disoproxil should not be co-administered with medicinal products that are strong CYP3A enzyme inducers as significant decreases in doravirine plasma concentrations are expected to occur, which may decrease the effectiveness of doravirine/lamivudine/tenofovir disoproxil (see sections 4.3 and 5.2).

Co-administration with the moderate CYP3A inducer rifabutin decreased doravirine concentrations (see Table 1). When Delstrigo is co-administered with rifabutin, a 100 mg dose of doravirine should be given daily, approximately 12 hours after doravirine/lamivudine/tenofovir disoproxil dose (see section 4.2).

Co-administration of doravirine/lamivudine/tenofovir disoproxil with other moderate CYP3A inducers has not been evaluated, but decreased doravirine concentrations are expected. If co-administration with other moderate CYP3A inducers (e.g., debrafenib, lesinurad, bosentan, thioridazine, nafcillin, modafinil, telotristat ethyl) cannot be avoided, a 100 mg dose of doravirine should be administered daily, approximately 12 hours after the administration of doravirine/lamivudine/tenofovir disoproxil dose (see section 4.2).

Co-administration of doravirine/lamivudine/tenofovir disproxil and medicinal products that are inhibitors of CYP3A may result in increased plasma concentrations of doravirine. However, no dose adjustment is needed when doravirine is co-administered with CYP3A inhibitors.

Lamivudine
Because lamivudine is primarily eliminated by the kidneys through a combination of glomerular filtration and active tubular secretion (see section 5.2), co-administration of doravirine/lamivudine/tenofovir disoproxil with medicinal products that reduce renal function or compete for active tubular secretion may increase serum concentrations of lamivudine.

Tenofovir disoproxil
Because tenofovir is primarily eliminated by the kidneys through a combination of glomerular filtration and active tubular secretion (see section 5.2), co-administration of doravirine/lamivudine/tenofovir disoproxil with medicinal products that reduce renal function or compete for active tubular secretion via OAT1, OAT3 or MRP4 may increase serum concentrations of tenofovir.

Due to the tenofovir disoproxil component of doravirine/lamivudine/tenofovir disoproxil, use of the product should be avoided with concurrent or recent use of nephrotoxic medicinal products. Some examples include, but are not limited to, acyclovir, cidofovir, ganciclovir, valacyclovir, valganciclovir, aminoglycosides (e.g., gentamicin), and high-dose or multiple NSAIDs (see section 4.4).

Effects of doravirine, lamivudine, and tenofovir disoproxil on other medicinal products

Doravirine
Doravirine at a dose of 100 mg once daily is not likely to have a clinically relevant effect on the plasma concentrations of medicinal products that are dependent on transport proteins for absorption and/or elimination or that are metabolised by CYP enzymes.

However, co-administration of doravirine and the sensitive CYP3A substrate midazolam resulted in a 18 % decrease in midazolam exposure, suggesting that doravirine may be a weak CYP3A inducer. Therefore, caution should be used when co-administering doravirine with medicinal products that are sensitive CYP3A substrates that also have a narrow therapeutic window (e.g., tacrolimus and sirolimus).

Lamivudine
Lamivudine does not inhibit or induce CYP enzymes.

Tenofovir
Based on the results of *in vitro* experiments and the known elimination pathway of tenofovir, the potential for CYP-mediated interactions involving tenofovir with other medicinal products is low.

Interaction table

Table 1 shows the established and other potential medicinal product interactions with the individual components of Delstrigo but is not all inclusive (increase is indicated as ↑, decrease is indicated as ↓, and no change as ↔). For potential medicinal product interactions with tenofovir disoproxil or lamivudine, (see sections 4.4 and 5.2).

Table 1: Interactions between the individual components of Delstrigo and other medicinal products

Medicinal product by therapeutic area	**Effects on medicinal product levels geometric mean ratio (90 % CI)***	**Recommendation concerning co-administration with doravirine/lamivudine/tenofovir disoproxil**
Acid-reducing agents		
antacid (aluminium and magnesium hydroxide oral suspension) (20 mL SD, doravirine 100 mg SD)	↔ doravirine AUC 1.01 (0.92, 1.11) C_{max} 0.86 (0.74, 1.01) C_{24} 1.03 (0.94, 1.12)	No dose adjustment is required.
pantoprazole (40 mg QD, doravirine 100 mg SD)	↓ doravirine AUC 0.83 (0.76, 0.91) C_{max} 0.88 (0.76, 1.01) C_{24} 0.84 (0.77, 0.92)	No dose adjustment is required.
omeprazole	Interaction not studied with doravirine or doravirine/lamivudine/tenofovir disoproxil. Expected: ↔ doravirine	No dose adjustment is required.
Angiotensin converting enzyme inhibitors		
lisinopril	Interaction not studied with doravirine or doravirine/lamivudine/tenofovir disoproxil. Expected: ↔ lisinopril	No dose adjustment is required.
Antiandrogens		
enzalutamide	Interaction not studied with doravirine or doravirine/lamivudine/tenofovir disoproxil. Expected: ↓ doravirine (Induction of CYP3A)	Co-administration is contraindicated.
Antibiotics		
nafcillin	Interaction not studied with doravirine or doravirine/lamivudine/tenofovir disoproxil. Expected: ↓ doravirine (Induction of CYP3A)	Co-administration should be avoided. If co-administration cannot be avoided, a 100 mg dose of doravirine should be taken daily, approximately12 h after the dose of doravirine/lamivudine/tenofovir disoproxil.

Medicinal product by therapeutic area	**Effects on medicinal product levels geometric mean ratio (90 % CI)***	**Recommendation concerning co-administration with doravirine/lamivudine/tenofovir disoproxil**
Anticonvulsants		
carbamazepine oxcarbazepine phenobarbital phenytoin	Interaction not studied with doravirine or doravirine/lamivudine/tenofovir disoproxil. Expected: ↓ doravirine (Induction of CYP3A)	Co-administration is contraindicated.
Antidiabetics		
metformin (1 000 mg SD, doravirine 100 mg QD)	↔ metformin AUC 0.94 (0.88, 1.00) C_{max} 0.94 (0.86, 1.03)	No dose adjustment is required.
canagliflozin liraglutide sitagliptin	Interaction not studied with doravirine or doravirine/lamivudine/tenofovir disoproxil. Expected: ↔ canagliflozin ↔ liraglutide ↔ sitagliptin	No dose adjustment is required.
Antidiarrhoeals		
telotristat ethyl	Interaction not studied with doravirine or doravirine/lamivudine/tenofovir disoproxil. Expected: ↓ doravirine (Induction of CYP3A)	Co-administration should be avoided. If co-administration cannot be avoided, a 100 mg dose of doravirine should be taken daily, 12 h after the dose of doravirine/lamivudine/tenofovir disoproxil.
Antigout and uricosuric agents		
lesinurad	Interaction not studied with doravirine or doravirine/lamivudine/tenofovir disoproxil. Expected: ↓ doravirine (Induction of CYP3A)	Co-administration should be avoided. If co-administration cannot be avoided, a 100 mg dose of doravirine should be taken daily, approximately 12 h after the dose of doravirine/lamivudine/tenofovir disoproxil.
Antimycobacterials		
Single dose rifampicin (600 mg SD, doravirine 100 mg SD) Multiple dose rifampicin (600 mg QD, doravirine 100 mg SD)	↔ doravirine AUC 0.91 (0.78, 1.06) C_{max} 1.40 (1.21, 1.63) C_{24} 0.90 (0.80, 1.01) ↓ doravirine AUC 0.12 (0.10, 0.15) C_{max} 0.43 (0.35, 0.52) C_{24} 0.03 (0.02, 0.04) (Induction of CYP3A)	Co-administration is contraindicated.

Medicinal product by therapeutic area	**Effects on medicinal product levels geometric mean ratio (90 % CI)***	**Recommendation concerning co-administration with doravirine/lamivudine/tenofovir disoproxil**
rifapentine	Interaction not studied with doravirine or doravirine/lamivudine/tenofovir disoproxil. Expected: ↓ doravirine (Induction of CYP3A)	Co-administration is contraindicated.
rifabutin (300 mg QD, doravirine 100 mg SD)	↓ doravirine AUC 0.50 (0.45, 0.55) C_{max} 0.99 (0.85, 1.15) C_{24} 0.32 (0.28, 0.35) (Induction of CYP3A)	If doravirine/ lamivudine/ tenofovir disoproxil is co-administered with rifabutin, a 100 mg dose of doravirine should be taken daily, approximately 12 h after dose of doravirine/lamivudine/tenofovir disoproxil.
Antineoplastics		
mitotane	Interaction not studied with doravirine or doravirine/lamivudine/tenofovir disoproxil. Expected: ↓ doravirine (Induction of CYP3A)	Co-administration is contraindicated.
Antipsychotics		
thioridazine	Interaction not studied with doravirine or doravirine/lamivudine/tenofovir disoproxil. Expected: ↓ doravirine (Induction of CYP3A)	Co-administration should be avoided. If co-administration cannot be avoided, a 100 mg dose of doravirine should be taken daily, approximately 12 h after the dose of doravirine/lamivudine/tenofovir disoproxil.
Azole antifungal agents		
ketoconazole (400 mg QD, doravirine 100 mg SD)	↑ doravirine AUC 3.06 (2.85, 3.29) C_{max} 1.25 (1.05, 1.49) C_{24} 2.75 (2.54, 2.98) (Inhibition of CYP3A)	No dose adjustment is required.
fluconazole itraconazole posaconazole voriconazole	Interaction not studied with doravirine or doravirine/lamivudine/tenofovir disoproxil. Expected: ↑ doravirine (Inhibition of CYP3A)	No dose adjustment is required.

Medicinal product by therapeutic area	**Effects on medicinal product levels geometric mean ratio (90 % CI)***	**Recommendation concerning co-administration with doravirine/lamivudine/tenofovir disoproxil**
Calcium channel blockers		
diltiazem verapamil	Interaction not studied with doravirine or doravirine/lamivudine/tenofovir disoproxil. Expected: ↑ doravirine (Inhibition of CYP3A)	No dose adjustment is required.
Cystic fibrosis treatment		
lumacaftor	Interaction not studied with doravirine or doravirine/lamivudine/tenofovir disoproxil. Expected: ↓ doravirine (Induction of CYP3A)	Co-administration is contraindicated.
Endothelin receptor antagonists		
bosentan	Interaction not studied with doravirine or doravirine/lamivudine/tenofovir disoproxil. Expected: ↓ doravirine (Induction of CYP3A)	Co-administration should be avoided. If co-administration cannot be avoided, a 100 mg dose of doravirine should be taken daily, approximately12 h after the dose of doravirine/lamivudine/tenofovir disoproxil.
Hepatitis C antiviral agents		
elbasvir + grazoprevir (50 mg elbasvir QD + 200 mg grazoprevir QD, doravirine 100 mg QD)	↑ doravirine AUC 1.56 (1.45, 1.68) C_{max} 1.41 (1.25, 1.58) C_{24} 1.61 (1.45, 1.79) (Inhibition of CYP3A) ↔ elbasvir AUC 0.96 (0.90, 1.02) C_{max} 0.96 (0.91, 1.01) C_{24} 0.96 (0.89, 1.04) ↔ grazoprevir AUC 1.07 (0.94, 1.23) C_{max} 1.22 (1.01, 1.47) C_{24} 0.90 (0.83, 0.96)	No dose adjustment is required.

Medicinal product by therapeutic area	**Effects on medicinal product levels geometric mean ratio (90 % CI)***	**Recommendation concerning co-administration with doravirine/lamivudine/tenofovir disoproxil**
ledipasvir + sofosbuvir (90 mg ledipasvir SD + 400 mg sofosbuvir SD, doravirine 100 mg SD)	↑ doravirine AUC 1.15 (1.07, 1.24) C_{max} 1.11 (0.97, 1.27) C_{24} 1.24 (1.13, 1.36) ↔ ledipasvir AUC 0.92 (0.80, 1.06) C_{max} 0.91 (0.80, 1.02) ↔ sofosbuvir AUC 1.04 (0.91, 1.18) C_{max} 0.89 (0.79, 1.00) ↔ GS-331007 AUC 1.03 (0.98, 1.09) C_{max} 1.03 (0.97, 1.09) Expected: ↑ tenofovir	Patients receiving doravirine/lamivudine/tenofovirdisoproxil concomitantly with ledipasvir/sofosbuvir should be monitored for adverse reactions associated with tenofovir disoproxil.
sofosbuvir/velpatasvir	Interaction not studied with doravirine or doravirine/lamivudine/tenofovir disoproxil. Expected: ↔ doravirine ↑ tenofovir	Patients receiving doravirine/lamivudine/tenofovir disoproxil concomitantly with sofosbuvir/velpatasvir should be monitored for adverse reactions associated with tenofovir disoproxil.
sofosbuvir	Interaction not studied with doravirine or doravirine/lamivudine/tenofovir disoproxil. Expected: ↔ doravirine	No dose adjustment is required.
daclatasvir	Interaction not studied with doravirine or doravirine/lamivudine/tenofovir disoproxil. Expected: ↔ doravirine	No dose adjustment is required.
ombitasvir/paritaprevir/ ritonavir and dasabuvir +/- ritonavir	Interaction not studied with doravirine or doravirine/lamivudine/tenofovir disoproxil. Expected: ↑ doravirine (Inhibition of CYP3A due to ritonavir)	No dose adjustment is required.

Medicinal product by therapeutic area	**Effects on medicinal product levels geometric mean ratio (90 % CI)***	**Recommendation concerning co-administration with doravirine/lamivudine/tenofovir disoproxil**
dasabuvir	Interaction not studied with doravirine or doravirine/lamivudine/tenofovir disoproxil. Expected: ↔ doravirine	No dose adjustment is required.
glecaprevir, pibrentasvir	Interaction not studied with doravirine or doravirine/lamivudine/tenofovir disoproxil. Expected: ↑ doravirine (inhibition of CYP3A)	No dose adjustment is required.
ribavirin	Interaction not studied with doravirine or doravirine/lamivudine/tenofovir disoproxil. Expected: ↔ doravirine	No dose adjustment is required.
Herbal supplements		
St. John's wort (*Hypericum perforatum)*	Interaction not studied with doravirine or doravirine/lamivudine/tenofovir disoproxil. Expected: ↓ doravirine (Induction of CYP3A)	Co-administration is contraindicated.
HIV antiviral agents		
tenofovir disoproxil (300 mg QD, doravirine 100 mg SD)	↔ doravirine AUC 0.95 (0.80, 1.12) C_{max} 0.80 (0.64, 1.01) C_{24} 0.94 (0.78, 1.12)	No dose adjustment is required.
lamivudine + tenofovir disoproxil (300 mg lamivudine SD + 245 mg tenofovir disoproxil SD, doravirine 100 mg SD)	↔ doravirine AUC 0.96 (0.87, 1.06) C_{max} 0.97 (0.88, 1.07) C_{24} 0.94 (0.83, 1.06) ↔lamivudine AUC 0.94 (0.88, 1.00) C_{max} 0.92 (0.81, 1.05) ↔ tenofovir AUC 1.11 (0.97, 1.28) C_{max} 1.17 (0.96, 1.42)	No dose adjustment is required.

Medicinal product by therapeutic area	**Effects on medicinal product levels geometric mean ratio (90 % CI)***	**Recommendation concerning co-administration with doravirine/lamivudine/tenofovir disoproxil**
Immunosuppressants		
tacrolimus sirolimus	Interaction not studied with doravirine or doravirine/lamivudine/tenofovir disoproxil. Expected: ↔ doravirine ↓ tacrolimus, sirolimus (Induction of CYP3A)	Monitor blood concentrations of tacrolimus and sirolimus as the dose of these agents may need to be adjusted.
Kinase inhibitors		
dabrafenib	Interaction not studied with doravirine or doravirine/lamivudine/tenofovir disoproxil. Expected: ↓ doravirine (Induction of CYP3A)	Co-administration should be avoided. If co-administration cannot be avoided, a 100 mg dose of doravirine should be taken daily, approximately 12 h after the dose of doravirine/lamivudine/tenofovir disoproxil.
Miscellaneous		
sorbitol solution (3.2 g, 10.2 g, 13.4 g)/lamivudine	Single dose lamivudine oral solution 300 mg lamivudine AUC ↓ 14 %; 32 %; 35 % C_{max} ↓ 28 %; 52 %; 55 %	When possible, avoid chronic co-administration of doravirine/lamivudine/tenofovir disoproxil with medicinal products containing sorbitol or other osmotic acting poly-alcohols (e.g., xylitol, mannitol, lactitol, maltitol). Consider more frequent monitoring of HIV-1 viral load when chronic co-administration cannot be avoided.
Opioid analgesics		
methadone (20-200 mg QD individualised dose, doravirine 100 mg QD)	↓ doravirine AUC 0.74 (0.61, 0.90) C_{max} 0.76 (0.63, 0.91) C_{24} 0.80 (0.63, 1.03) ↔ R-methadone AUC 0.95 (0.90, 1.01) C_{max} 0.98 (0.93, 1.03) C_{24} 0.95 (0.88, 1.03) ↔ S-methadone AUC 0.98 (0.90, 1.06) C_{max} 0.97 (0.91, 1.04) C_{24} 0.97 (0.86, 1.10)	No dose adjustment is required.

Medicinal product by therapeutic area	**Effects on medicinal product levels geometric mean ratio (90 % CI)***	**Recommendation concerning co-administration with doravirine/lamivudine/tenofovir disoproxil**
buprenorphine naloxone	Interaction not studied with doravirine or doravirine/lamivudine/tenofovir disoproxil. Expected: ↔ buprenorphine ↔ naloxone	No dose adjustment is required.
Oral contraceptives		
0.03 mg ethinyl oestradiol/ 0.15 mg levonorgestrel SD, doravirine 100 mg QD	↔ ethinyl oestradiol AUC 0.98 (0.94, 1.03) C_{max} 0.83 (0.80, 0.87) ↑ levonorgestrel AUC 1.21 (1.14, 1.28) C_{max} 0.96 (0.88, 1.05)	No dose adjustment is required.
norgestimate/ethinyl oestradiol	Interaction not studied with doravirine or doravirine/lamivudine/tenofovir disoproxil. Expected: ↔ norgestimate/ethinyl oestradiol	No dose adjustment is required.
Psychostimulants		
modafinil	Interaction not studied with doravirine or doravirine/lamivudine/tenofovir disoproxil. Expected: ↓ doravirine (Induction of CYP3A)	Co-administration should be avoided. If co-administration cannot be avoided, a 100 mg dose of doravirine should be taken daily, approximately12 h after the dose of doravirine/lamivudine/tenofovir disoproxil.
Sedatives/Hypnotics		
midazolam (2 mg SD, doravirine 120 mg QD)	↓ midazolam AUC 0.82 (0.70, 0.97) C_{max} 1.02 (0.81, 1.28)	No dose adjustment is required.
Statins		
atorvastatin (20 mg SD, doravirine 100 mg QD)	↔ atorvastatin AUC 0.98 (0.90, 1.06) C_{max} 0.67 (0.52, 0.85)	No dose adjustment is required.
rosuvastatin simvastatin	Interaction not studied with doravirine or doravirine/lamivudine/tenofovir disoproxil. Expected: ↔ rosuvastatin ↔ simvastatin	No dose adjustment is required.
↑ = increase, ↓ = decrease, ↔ = no change CI = Confidence Interval; SD = Single Dose; QD = Once Daily; BID = Twice Daily *$AUC_{0-\infty}$ for single dose, AUC_{0-24} for once daily.		

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no or limited amount of data from the use of doravirine in pregnant women. A large amount of data on pregnant women (more than 3 000 outcomes from first trimester) taking the individual active component lamivudine in combination with other antiretrovirals indicates no malformative toxicity. A moderate amount of data on pregnant women (between 300-1 000 pregnancy outcomes) indicate no malformations or foetal/neonatal toxicity associated with tenofovir disoproxil.

Antiretroviral pregnancy registry
To monitor maternal-foetal outcomes in patients exposed to antiretroviral medicinal products while pregnant, an Antiretroviral Pregnancy Registry has been established. Physicians are encouraged to register patients in this registry.

Animal studies with doravirine do not indicate direct or indirect harmful effects with respect to reproductive toxicity (see section 5.3).

Animal studies with tenofovir disoproxil do not indicate direct or indirect harmful effects of tenofovir disoproxil with respect to reproductive toxicity (see section 5.3).

Animal studies with lamivudine showed an increase in early embryonic deaths in rabbits but not in rats (see section 5.3). Placental transfer of lamivudine has been shown to occur in humans. Lamivudine may inhibit cellular DNA replication (see section 5.3). The clinical relevance of this finding is unknown.

As a precautionary measure, it is preferable to avoid the use of Delstrigo during pregnancy.

Breast-feeding

It is unknown whether doravirine is excreted in human milk. Available pharmacodynamic/toxicological data in animals have shown excretion of doravirine in milk (see section 5.3).

Lamivudine has been identified in breast-fed newborns/infants of treated women. Based on more than 200 mother/child pairs treated for HIV, serum concentrations of lamivudine in breast-fed infants of mothers treated for HIV are very low (< 4 % of maternal serum concentrations) and progressively decrease to undetectable levels when breast-fed infants reach 24 weeks of age. There are no data available on the safety of lamivudine when administered to babies less than three months old.

Tenofovir is excreted in human milk. There is insufficient information on the effects of tenofovir in newborns/infants.

It is recommended that women living with HIV do not breast-feed their infants in order to avoid transmission of HIV.

Fertility

No human data on the effect of Delstrigo on fertility are available. Animal studies do not indicate harmful effects of doravirine, lamivudine, or tenofovir disoproxil on fertility at exposure levels higher than the exposure in humans at the recommended clinical dose (see section 5.3).

4.7 Effects on ability to drive and use machines

Delstrigo has a minor influence on the ability to drive and use machines. Patients should be informed that fatigue, dizziness, and somnolence have been reported during treatment with Delstrigo (see

section 4.8). This should be considered when assessing a patient's ability to drive or operate machinery.

4.8 Undesirable effects

Summary of the safety profile

In phase 3 clinical trials with doravirine plus 2 nucleoside reverse transcriptase inhibitors (NRTIs), the most frequently reported adverse reactions were nausea (4 %) and headache (3 %).

Tabulated summary of adverse reactions

The adverse reactions with doravirine plus 2 NRTIs from Phase 3 clinical trials (DRIVE-FORWARD, DRIVE-SHIFT and DRIVE-AHEAD) and post-marketing experience are listed below by body system organ class and frequency. Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness. Frequencies are defined as very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1 000 to < 1/100), rare (≥ 1/10 000 to < 1/1 000), very rare (< 1/10 000), or not known (cannot be estimated from the available data).

Table 2: Tabulated summary of adverse reactions associated with doravirine/lamivudine/tenofovir disoproxil

Frequency	Adverse reactions
Infections and infestations	
Rare	rash pustular
Blood and lymphatic systems disorders	
Uncommon	neutropenia*, anaemia*, thrombocytopenia*
Very rare	pure red cell aplasia*
Metabolism and nutrition disorders	
Uncommon	hypophosphataemia, hypokalaemia*
Rare	hypomagnesaemia, lactic acidosis*
Psychiatric disorders	
Common	abnormal dreams, insomnia[1],
Uncommon	nightmare, depression[2], anxiety[3], irritability, confusional state, suicidal ideation
Rare	aggression, hallucination, adjustment disorder, mood altered, somnambulism
Nervous system disorders	
Common	headache, dizziness, somnolence
Uncommon	disturbance in attention, memory impairment, paraesthesia, hypertonia, poor quality sleep
Very rare	peripheral neuropathy (or paraesthesia)*
Vascular disorders	
Uncommon	hypertension
Respiratory, thoracic and mediastinal disorders	
Common	cough*, nasal symptoms*
Rare	dyspnoea, tonsillar hypertrophy
Gastrointestinal disorders	
Common	nausea, diarrhoea, abdominal pain[4], vomiting, flatulence
Uncommon	constipation, abdominal discomfort[5], abdominal distension, dyspepsia, faeces soft[6], gastrointestinal motility disorder[7], pancreatitis*
Rare	rectal tenesmus
Hepatobiliary disorders	
Rare	hepatic steatosis*, hepatitis[†]

Frequency	Adverse reactions
Skin and subcutaneous tissue disorders	
Common	alopecia*, rash[8]
Uncommon	pruritus
Rare	dermatitis allergic, rosacea, angioedema*
Not known	toxic epidermal necrolysis
Musculoskeletal and connective tissue disorders	
Common	muscle disorders*, bone mineral density decreased*
Uncommon	myalgia, arthralgia, rhabdomyolysis*‡, muscular weakness*‡
Rare	musculoskeletal pain, osteomalacia (manifested as bone pain and infrequently contributing to fractures)*, myopathy*
Renal and urinary disorders	
Uncommon	increased creatinine*, proximal renal tubulopathy (including Fanconi syndrome)*
Rare	acute kidney injury, renal disorder, calculus urinary, nephrolithiasis, acute renal failure*, renal failure*, acute tubular necrosis*, nephritis (including acute interstitial)*, nephrogenic diabetes insipidus*
General disorders and administration site conditions	
Common	fatigue, fever*
Uncommon	asthenia, malaise
Rare	chest pain, chills, pain, thirst
Investigations	
Common	alanine aminotransferase increased[9]
Uncommon	aspartate aminotransferase increased, lipase increased, amylase increased, haemoglobin decreased
Rare	blood creatine phosphokinase increased

*This adverse reaction was not identified as an adverse reaction associated with doravirine from the Phase 3 clinical studies (DRIVE-FORWARD, DRIVE-AHEAD, DRIVE-SHIFT), but is included in this table as an adverse reaction based on the Summary of Product Characteristics (SmPC) of 3TC and/or TDF. The highest frequency category reported in the 3TC or TDF SmPC is used.

†This adverse reaction was not identified as an adverse reaction associated with doravirine from the Phase 3 clinical studies (DRIVE-FORWARD, DRIVE-AHEAD, DRIVE-SHIFT), but was seen during post-marketing use of doravirine-containing regimens and is an adverse reaction listed in the SmPC of 3TC and TDF. The highest frequency category reported in the 3TC and TDF SmPCs is used.

‡This adverse reaction may occur as a consequence of proximal renal tubulopathy. It is not considered to be causally associated with tenofovir disoproxil in the absence of this condition.

[1]insomnia includes: insomnia, initial insomnia and sleep disorder.

[2]depression includes: depression, depressed mood, major depression, and persistent depressive disorder.

[3]anxiety includes: anxiety and generalised anxiety disorder.

[4]abdominal pain includes: abdominal pain, and abdominal pain upper.

[5]abdominal discomfort includes: abdominal discomfort, and epigastric discomfort.

[6]faeces soft includes: faeces soft and abnormal faeces.

[7]gastrointestinal motility disorder includes: gastrointestinal motility disorder, and frequent bowel movements.

[8]rash includes: rash, rash macular, rash erythematous, rash generalised, rash maculo-papular, rash papular, and urticarial.

[9]alanine aminotransferase increased includes: alanine aminotransferase increased and hepatocellular injury.

Description of selected adverse reactions

Immune reactivation syndrome

In HIV-infected patients with severe immune deficiency at the time of initiation of combination antiretroviral therapy (CART), an inflammatory reaction to asymptomatic or residual opportunistic infections may arise. Autoimmune disorders (such as Graves' disease and autoimmune hepatitis) have also been reported; however, the reported time to onset is more variable and these events can occur many months after initiation of treatment (see section 4.4).

Lactic acidosis

Cases of lactic acidosis have been reported with tenofovir disoproxil alone or in combination with other antiretrovirals. Patients with predisposing factors such as patients with decompensated liver disease, or patients receiving concomitant medicinal products known to induce lactic acidosis are at increased risk of experiencing severe lactic acidosis during tenofovir disoproxil treatment, including fatal outcomes.

Severe cutaneous adverse reactions (SCARs)

Severe cutaneous adverse reactions (SCARs), such as toxic epidermal necrolysis (TEN), have been reported in association with doravirine-containing treatment regimens (see section 4.4).

Paediatric population

The safety of doravirine/lamivudine/tenofovir disoproxil was evaluated in 45 HIV-1 infected virologically suppressed or treatment-naïve paediatric patients 12 to less than 18 years of age through Week 48 in an open-label trial (IMPAACT 2014 (Protocol 027)). The safety profile in paediatric subjects was similar to that in adults.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

Doravirine

There is no information on potential acute symptoms and signs of overdose with doravirine.

Lamivudine

Because a negligible amount of lamivudine was removed via (4-hour) haemodialysis, continuous ambulatory peritoneal dialysis, and automated peritoneal dialysis, it is not known if continuous haemodialysis would provide clinical benefit in a lamivudine overdose event.

Tenofovir disoproxil

Tenofovir disoproxil is efficiently removed by haemodialysis with an extraction coefficient of approximately 54 %. Following a single 245 mg dose of tenofovir disoproxil, a 4-hour haemodialysis session removed approximately 10 % of the administered tenofovir dose.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antivirals for systemic use, ATC code: J05AR24

Mechanism of action

Doravirine
Doravirine is a pyridinone non-nucleoside reverse transcriptase inhibitor of HIV-1 and inhibits HIV-1 replication by non-competitive inhibition of HIV-1 reverse transcriptase (RT). Doravirine does not inhibit the human cellular DNA polymerases α, ß, and mitochondrial DNA polymerase γ.

Lamivudine
Lamivudine is a nucleoside analogue. Intracellularly, lamivudine is phosphorylated to its active 5′- triphosphate metabolite, lamivudine triphosphate (3TC-TP). The principal mode of action of 3TC-TP is inhibition of RT via DNA chain termination after incorporation of the nucleotide analogue.

Tenofovir disoproxil
Tenofovir disoproxil is an acyclic nucleoside phosphonate diester analogue of adenosine monophosphate. Tenofovir disoproxil requires initial diester hydrolysis for conversion to tenofovir and subsequent phosphorylations by cellular enzymes to form tenofovir diphosphate. Tenofovir diphosphate inhibits the activity of HIV-1 RT by competing with the natural substrate deoxyadenosine 5′-triphosphate and, after incorporation into DNA, by DNA chain termination. Tenofovir diphosphate is a weak inhibitor of mammalian DNA polymerases α, β, and mitochondrial DNA polymerase γ.

Antiviral activity in cell culture

Doravirine
Doravirine exhibited an EC_{50} value of 12.0±4.4 nM against wild-type laboratory strains of HIV-1 when tested in the presence of 100 % normal human serum using MT4-GFP reporter cells. Doravirine demonstrated antiviral activity against a broad panel of primary HIV-1 isolates (A, A1, AE, AG, B, BF, C, D, G, H) with EC_{50} values ranging from 1.2 nM to 10.0 nM. The antiviral activity of doravirine was not antagonistic when combined with lamivudine and tenofovir disoproxil.

Lamivudine
The antiviral activity of lamivudine against HIV-1 was assessed in a number of cell lines including monocytes and peripheral blood mononuclear cells (PBMCs) using standard susceptibility assays. EC_{50} values were in the range of 0.003 to 15 microM (1 microM = 0.23 micrograms per mL). The median EC_{50} values of lamivudine were 60 nM (range: 20 to 70 nM), 35 nM (range: 30 to 40 nM), 30 nM (range: 20 to 90 nM), 20 nM (range: 3 to 40 nM), 30 nM (range: 1 to 60 nM), 30 nM (range: 20 to 70 nM), 30 nM (range: 3 to 70 nM), and 30 nM (range: 20 to 90 nM) against HIV-1 clades A-G and group O viruses (n = 3 except n = 2 for clade B) respectively. Ribavirin (50 microM) used in the treatment of chronic HCV infection decreased the anti-HIV-1 activity of lamivudine by 3.5-fold in MT-4 cells.

Tenofovir disoproxil
The antiviral activity of tenofovir against laboratory and clinical isolates of HIV-1 was assessed in T lymphoblastoid cell lines, primary monocyte/macrophage cells and peripheral blood lymphocytes. The EC_{50} values for tenofovir were in the range of 0.04-8.5 microM. Tenofovir displayed antiviral activity in cell culture against HIV-1 clades A, B, C, D, E, F, G, and O (EC_{50} values ranged from 0.5-2.2 microM).

Resistance

In cell culture
Doravirine
Doravirine-resistant strains were selected in cell culture starting from wild-type HIV-1 of different origins and subtypes, as well as NNRTI-resistant HIV-1. Observed emergent amino acid substitutions in RT included: V106A, V106M, V106I, V108I, F227L, F227C, F227I, F227V, H221Y, M230I, L234I, P236L, and Y318F. The V106A, V106M, V108I, H221Y, F227C, M230I, P236L, and Y318F substitutions conferred 3.4-fold to 70-fold reductions in susceptibility to doravirine. Y318F in combination with V106A, V106M, V108I, or F227C conferred greater decreases in susceptibility to doravirine than Y318F alone, which conferred a 10-fold reduction in susceptibility to doravirine. Common NNRTI-resistant mutations (K103N, Y181C) were not selected in the *in vitro* study. V106A (yielding a fold change of around 19) appeared as an initial substitution in subtype B virus, and V106A or M in subtype A and C virus. Subsequently F227(L/C/V) or L234I emerged in addition to V106 substitutions (double mutants yielding a fold change of > 100).

Lamivudine
Lamivudine-resistant variants of HIV-1 have been selected in cell culture and in subjects treated with lamivudine. Genotypic analysis showed that the resistance was due to a specific amino acid substitution in the HIV-1 RT at codon 184 changing the methionine to either isoleucine or valine (M184V/I).

Tenofovir disoproxil
HIV-1 isolates selected by tenofovir expressed a K65R substitution in HIV-1 RT and showed a 2-4 fold reduction in susceptibility to tenofovir. In addition, a K70E substitution in HIV-1 RT has been selected by tenofovir and results in low-level reduced susceptibility to abacavir, emtricitabine, lamivudine, and tenofovir.

In clinical trials
Treatment-naïve adult subjects
Doravirine
The Phase 3 studies, DRIVE-FORWARD and DRIVE-AHEAD, included previously untreated patients (n = 747) where the following NNRTI substitutions were part of exclusion criteria: L100I, K101E, K101P, K103N, K103S, V106A, V106I, V106M, V108I, E138A, E138G, E138K, E138Q, E138R, V179L, Y181C, Y181I, Y181V, Y188C, Y188H, Y188L, G190A, G190S, H221Y, L234I, M230I, M230L, P225H, F227C, F227L, F227V.

The following de novo resistance was seen in the resistance analysis subset (subjects with HIV-1 RNA greater than 400 copies per mL at virologic failure or at early study discontinuation and having resistance data).

Table 3: Resistance development up to Week 96 in protocol defined virologic failure population + early discontinuation population

	DRIVE-FORWARD		DRIVE-AHEAD	
	DOR + NRTIs* (383)	DRV+r + NRTIs* (383)	DOR/TDF/3TC (364)	EFV/TDF/FTC (364)
Successful genotype, n	15	18	32	33
Genotypic resistance to				
DOR or control (DRV or EFV)	2 (DOR)	0 (DRV)	8 (DOR)	14 (EFV)
NRTI backbone	2†	0	6	5
M184I/V only	2	0	4	4
K65R only	0	0	1	0
K65R + M184I/V	0	0	1	1

*NRTI in DOR arm: FTC/TDF (333) or ABC/3TC (50); NRTI in DRV+r arm: FTC/TDF (335) or ABC/3TC (48)
†Subjects received FTC/TDF
ABC=abacavir; FTC=emtricitabine; DRV=darunavir; r=ritonavir

Emergent doravirine associated resistance substitutions in RT included one or more of the following: A98G, V106I, V106A, V106M/T, Y188L, H221Y, P225H, F227C, F227C/R, and Y318Y/F.

Virologically suppressed adult subjects
The DRIVE-SHIFT study included virologically suppressed patients (N=670) with no history of treatment failure (see section, Clinical experience). A documented absence of genotypic resistance (prior to starting first therapy) to doravirine, lamivudine, and tenofovir was part of the inclusion criteria for patients who switched from a PI- or INI-based regimen. Exclusionary NNRTI substitutions were those listed above (DRIVE-FORWARD and DRIVE-AHEAD), with the exception of substitutions RT K103N, G190A and Y181C (accepted in DRIVE-SHIFT). Documentation of pre-treatment resistance genotyping was not required for patients who switched from a NNRTI-based regimen.

In the DRIVE-SHIFT clinical trial, no subjects developed genotypic or phenotypic resistance to DOR, 3TC, or TDF during the initial 48 weeks (immediate switch, N=447) or 24 weeks (delayed switch, N=209) of treatment with Delstrigo. One subject developed RT M184M/I mutation and phenotypic resistance to 3TC and FTC during treatment with their baseline regimen. None of the 24 subjects (11 in the immediate switch group, 13 in the delayed switch group) with baseline NNRTI mutations (RT K103N, G190A, or Y181C) experienced virologic failure through Week 48, or at time of discontinuation.

Paediatric subjects
In the IMPAACT 2014 (Protocol 027) clinical trial, no subject who was virologically suppressed at baseline met the criteria for resistance analysis. One treatment-naïve subject who met the protocol-defined virologic failure criteria (defined as 2 consecutive plasma HIV-1 RNA test results ≥200 copies/mL at or after Week 24) was evaluated for the development of resistance; no emergence of genotypic or phenotypic resistance to doravirine, lamivudine or tenofovir was detected.

Cross-resistance

No significant cross-resistance has been demonstrated between doravirine-resistant HIV-1 variants and lamivudine/emtricitabine or tenofovir or between lamivudine- or tenofovir-resistant variants and doravirine.

Doravirine
Doravirine has been evaluated in a limited number of patients with NNRTI resistance (K103N n = 7, G190A n = 1); all patients were suppressed to < 40 copies/mL at Week 48. A breakpoint for a

reduction in susceptibility, yielded by various NNRTI substitutions, that is associated with a reduction in clinical efficacy has not been established.

Laboratory strains of HIV-1 harbouring the common NNRTI-associated mutations K103N, Y181C, or K103N/Y181C substitutions in RT exhibit less than a 3-fold decrease in susceptibility to doravirine compared to wild-type virus when evaluated in the presence of 100 % normal human serum. In *in vitro* studies, doravirine was able to suppress the following NNRTI-associated substitutions; K103N, Y181C, and G190A under clinically relevant concentrations.

A panel of 96 diverse clinical isolates containing NNRTI-associated mutations was evaluated for susceptibility to doravirine in the presence of 10 % foetal bovine serum. Clinical isolates containing the Y188L substitution or V106 substitutions in combination with A98G, H221Y, P225H, F227C or Y318F showed a greater than 100-fold reduced susceptibility to doravirine. Other substitutions yielded a fold change of 5-10 (G190S (5.7); K103N/P225H (7.9), V108I/Y181C (6.9), Y181V (5.1)). The clinical relevance of a 5-10 fold reduction in susceptibility is unknown.

Treatment emergent doravirine resistance associated substitutions may confer cross-resistance to efavirenz, rilpivirine, nevirapine, and etravirine. Of the 8 subjects who developed high level doravirine resistance in the pivotal studies, 6 had phenotypic resistance to EFV and nevirapine, 3 to rilpivirine, and 3 had partial resistance to etravirine based on the Monogram Phenosense assay.

Lamivudine
Cross-resistance has been observed among NRTIs. The M184I/V lamivudine resistance substitution confers resistance to emtricitabine. Lamivudine-resistant HIV-1 mutants were also cross resistant to didanosine (ddI). In some subjects treated with zidovudine plus didanosine, isolates resistant to multiple RT inhibitors, including lamivudine, have emerged.

Tenofovir disoproxil
Cross-resistance has been observed among NRTIs. The K65R substitution in HIV-1 RT selected by tenofovir is also selected in some HIV-1 infected patients treated with abacavir or didanosine. HIV-1 isolates with the K65R substitution also showed reduced susceptibility to emtricitabine and lamivudine. Therefore, cross-resistance among these NRTIs may occur in patients whose virus harbours the K65R substitution. The K70E substitution selected clinically by tenofovir disoproxil results in reduced susceptibility to abacavir, didanosine, emtricitabine, lamivudine, and tenofovir. HIV-1 isolates from patients (n = 20) whose HIV-1 expressed a mean of 3 zidovudine associated RT amino acid substitutions (M41L, D67N, K70R, L210W, T215Y/F, or K219Q/E/N) showed a 3.1-fold decrease in the susceptibility to tenofovir. Subjects whose virus expressed an L74V RT substitution without zidovudine resistance-associated substitutions (n = 8) had reduced response to tenofovir disoproxil. Limited data are available for patients whose virus expressed a Y115F substitution (n = 3), Q151M substitution (n = 2), or T69 insertion (n = 4) in HIV-1 RT, all of whom had a reduced response in clinical trials.

Clinical experience

Treatment-naïve adult subjects
The efficacy of doravirine is based on the analyses of 96-week data from two randomised, multicentre, double-blind, active controlled Phase 3 trials, (DRIVE-FORWARD and DRIVE-AHEAD) in antiretroviral treatment-naïve, HIV-1 infected subjects (n = 1 494). Refer to Resistance section for NNRTI substitutions that were part of exclusion criteria.

In DRIVE-FORWARD, 766 subjects were randomised and received at least 1 dose of either doravirine 100 mg or darunavir + ritonavir 800+100 mg once daily, each in combination with emtricitabine/tenofovir disoproxil (FTC/TDF) or abacavir/lamivudine (ABC/3TC) selected by the investigator. At baseline, the median age of subjects was 33 years (range 18 to 69 years), 86 % had $CD4^+$ T cell count greater than 200 cells per mm^3, 84 % were male, 27 % were non-white, 4 % had hepatitis B and/or C virus co-infection, 10 % had a history of AIDS, 20 % had HIV-1 RNA greater

than 100 000 copies per mL, 13 % received ABC/3TC and 87 % received FTC/TDF; these characteristics were similar between treatment groups.

In DRIVE-AHEAD, 728 subjects were randomised and received at least 1 dose of either doravirine/lamivudine/tenofovir disoproxil 100/300/245 mg (DOR/3TC/TDF) or efavirenz/emtricitabine/tenofovir disoproxil (EFV/FTC/TDF) once daily. At baseline, the median age of subjects was 31 years (range 18-70 years), 85 % were male, 52 % were non-white, 3 % had hepatitis B or C co-infection, 14 % had a history of AIDS, 21 % had HIV-1 RNA > 100 000 copies per mL, and 12 % had $CD4^+$ T cell count < 200 cells per mm^3; these characteristics were similar between treatment groups.

Week 48 and 96 outcomes for DRIVE-FORWARD and DRIVE-AHEAD are provided in Table 4. The doravirine-based regimens demonstrated consistent efficacy across demographic and baseline prognostic factors.

Table 4: Efficacy response (< 40 copies/mL, Snapshot approach) in the pivotal studies

	DRIVE-FORWARD		**DRIVE-AHEAD**	
	DOR + 2 NRTIs (383)	**DRV+r + 2 NRTIs (383)**	**DOR/3TC/TDF (364)**	**EFV/FTC/TDF (364)**
Week 48	83 %	79 %	84 %	80 %
Difference (95 % CI)	4.2 % (-1.4%, 9.7 %)		4.1 % (-1.5 %, 9.7 %)	
Week 96*	72 % (N=379)	64 % (N=376)	76 % (N=364)	73 % (N=364)
Difference (95 % CI)	7.6 % (1.0 %, 14.2 %)		3.3 % (-3.1 %, 9.6 %)	
Week 48 outcome (< 40 copies/mL) by baseline factors				
HIV-1 RNA copies/mL				
≤ 100 000	256/285 (90 %)	248/282 (88 %)	251/277 (91 %)	234/258 (91 %)
> 100 000	63/79 (80 %)	54/72 (75 %)	54/69 (78 %)	56/73 (77 %)
CD4 count, cells/μL				
≤ 200	34/41 (83 %)	43/61 (70 %)	27/42 (64 %)	35/43 (81 %)
> 200	285/323 (88 %)	260/294 (88 %)	278/304 (91 %)	255/288 (89 %)
NRTI background therapy				
TDF/FTC	276/316 (87 %)	267/312 (86 %)	NA	
ABC/3TC	43/48 (90 %)	36/43 (84 %)	NA	
Viral subtype				
B	222/254 (87 %)	219/255 (86 %)	194/222 (87 %)	199/226 (88 %)
non-B	97/110 (88 %)	84/100 (84 %)	109/122 (89 %)	91/105 (87 %)
Mean CD4 change from baseline				
Week 48	193	186	198	188
Week 96	224	207	238	223

*For Week 96, certain subjects with missing HIV-1 RNA were excluded from the analysis.

Virologically suppressed adult subjects
The efficacy of switching from a baseline regimen consisting of two nucleoside reverse transcriptase inhibitors in combination with a ritonavir- or cobicistat-boosted PI, or cobicistat-boosted elvitegravir,

or an NNRTI to Delstrigo was evaluated in a randomised, open-label trial (DRIVE-SHIFT), in virologically suppressed HIV-1 infected adults. Subjects must have been virologically suppressed (HIV-1 RNA < 40 copies/mL) on their baseline regimen for at least 6 months prior to trial entry, with no history of virologic failure, and a documented absence of RT substitutions conferring resistance to doravirine, lamivudine and tenofovir (see section, Resistance). Subjects were randomised to either switch to Delstrigo at baseline [N= 447, Immediate Switch Group (ISG)], or stay on their baseline regimen until Week 24, at which point they switched to Delstrigo [N= 223, Delayed Switch Group (DSG)]. At baseline, the median age of subjects was 43 years, 16 % were female, and 24 % were non-white.

In the DRIVE-SHIFT trial, an immediate switch to Delstrigo was demonstrated to be non-inferior at Week 48 compared to continuation of the baseline regimen at Week 24 as assessed by the proportion of subjects with HIV-1 RNA < 40 copies/mL. Treatment results are shown in Table 5. Consistent results were seen for the comparison at study Week 24 in each treatment group.

Table 5: Efficacy response (Snapshot approach) in the DRIVE-SHIFT study

Outcome	Delstrigo Once Daily ISG Week 48 N=447	Baseline Regimen DSG Week 24 N=223
HIV-1 RNA < 40 copies/mL	90 %	93 %
ISG-DSG, Difference (95 % CI)*	-3.6 % (-8.0 %, 0.9 %)	
Proportion (%) of Subjects With HIV-1 RNA < 40 copies/mL by Baseline Regimen Received		
Ritonavir- or Cobicistat- boosted PI	280/316 (89 %)	145/156 (93 %)
Cobicistat-boosted elvitegravir	23/25 (92 %)	11/12 (92 %)
NNRTI	98/106 (92 %)	52/55 (95 %)
Proportion (%) of Subjects With HIV-1 RNA < 40 copies/mL by Baseline $CD4^+$ T cell Count ($cells/mm^3$)		
< 200 $cells/mm^3$	10/13 (77 %)	3/4 (75 %)
≥ 200 $cells/mm^3$	384/426 (90 %)	202/216 (94 %)
HIV-1 RNA ≥ 40 copies/mL†	3 %	4 %
No Virologic Data Within the Time Window	8 %	3 %
Discontinued study due to AE or Death‡	3 %	0
Discontinued study for Other Reasons§	4 %	3 %
On study but missing data in window	0	0

*The 95 % CI for the treatment difference was calculated using stratum-adjusted Mantel-Haenszel method.

†Includes subjects who discontinued study treatment or study before Week 48 for ISG or before Week 24 for DSG for lack or loss of efficacy and subjects with HIV-1 RNA ≥ 40 copies/mL in the Week 48 window for ISG and in the Week 24 window for DSG.

‡Includes subjects who discontinued because of adverse event (AE) or death if this resulted in no virologic data on treatment during the specified window.

§Other reasons include: lost to follow-up, non-compliance with study treatment, physician decision, protocol deviation, withdrawal by subject.

Baseline regimen = ritonavir or cobicistat-boosted PI (specifically atazanavir, darunavir, or lopinavir), or cobicistat-boosted elvitegravir, or NNRTI (specifically efavirenz, nevirapine, or rilpivirine), each administered with two NRTIs.

Discontinuation due to adverse events

In DRIVE-AHEAD, a lower proportion of subjects who discontinued due to an adverse event by Week 48 was seen for the Delstrigo group (3.0 %) compared with the EFV/FTC/TDF group (6.6 %).

Paediatric population

The efficacy of DOR/3TC/TDF was evaluated in an open-label, single-arm trial in HIV-1 infected paediatric patients 12 to less than 18 years of age (IMPAACT 2014 (Protocol 027)).

At baseline, the median age of subjects was 15 years (range: 12 to 17), 58% were female, 78% were Asian and 22% were Black, and the median CD4+ T-cell count was 713 cells per mm^3 (range: 84 to 1,397). After switching to DOR/3TC/TDF, 95% (41/43) of virologically-suppressed subjects remained suppressed (HIV-1 RNA < 50 copies/mL) at Week 24 and 93% (40/43) remained suppressed (HIV-1 RNA < 50 copies/mL) at Week 48.

The European Medicines Agency has deferred the obligation to submit the results of studies with Delstrigo in one or more subsets of the paediatric population in treatment of human immunodeficiency virus-1 (HIV-1) infection. See section 4.2 for information on paediatric use.

5.2 Pharmacokinetic properties

Single-dose administration of one doravirine/lamivudine/tenofovir disoproxil tablet to healthy subjects (N = 24) under fasted conditions provided comparable exposures of doravirine, lamivudine, and tenofovir to administration of doravirine tablets (100 mg) plus lamivudine tablets (300 mg) plus tenofovir disoproxil tablets (245 mg). The administration of a single Delstrigo tablet with a high-fat meal to healthy subjects resulted in a 26 % increase in doravirine C_{24}, while AUC and C_{max} were not significantly affected. Lamivudine C_{max} decreased by 19 % with a high fat meal, while AUC was not significantly affected. Tenofovir C_{max} decreased by 12 % and AUC increased by 27 % with a high fat meal. These differences in pharmacokinetics are not clinically relevant.

Doravirine
The pharmacokinetics of doravirine were studied in healthy subjects and HIV-1-infected subjects. Doravirine pharmacokinetics are similar in healthy subjects and HIV-1-infected subjects. Steady state was generally achieved by Day 2 of once daily dosing, with accumulation ratios of 1.2 to 1.4 for AUC_{0-24}, C_{max}, and C_{24}. Doravirine steady state pharmacokinetics following administration of 100 mg once daily to HIV-1 infected subjects, based on a population pharmacokinetics analysis are provided below.

Parameter GM (%CV)	AUC_{0-24} µg•h/mL	C_{max} µg/mL	C_{24} µg/mL
Doravirine 100 mg once daily	16.1 (29)	0.962 (19)	0.396 (63)
GM: Geometric mean, %CV: Geometric coefficient of variation			

Absorption

Following oral dosing, peak plasma concentrations are achieved 2 hours after dosing. Doravirine has an estimated absolute bioavailability of approximately 64 % for the 100 mg tablet.

Distribution

Based on administration of an intravenous microdose, the volume of distribution of doravirine is 60.5 L. Doravirine is approximately 76 % bound to plasma proteins.

Biotransformation

Based on *in vitro* data, doravirine is primarily metabolised by CYP3A.

Elimination

Doravirine
Doravirine has a terminal half-life ($t_{1/2}$) of approximately 15 hours. Doravirine is primarily eliminated via oxidative metabolism mediated by CYP3A4. Biliary excretion of unchanged medicinal product may contribute to the elimination of doravirine, but this elimination route is not expected to be significant. Excretion of unchanged medicinal product via urinary excretion is minor.

Lamivudine
Following oral administration, lamivudine is rapidly absorbed and extensively distributed. After multiple-dose oral administration of lamivudine 300 mg once daily for 7 days to 60 healthy subjects, steady-state C_{max} ($C_{max,ss}$) was 2.04 ± 0.54 microgram per mL (mean ± SD) and the 24-hour steady-state AUC ($AUC_{24,ss}$) was 8.87 ± 1.83 mcg•hour per mL. Binding to plasma protein is low. Approximately 71 % of an intravenous dose of lamivudine is recovered as unchanged medicinal product in the urine. Metabolism of lamivudine is a minor route of elimination. In humans, the only known metabolite is the trans-sulphoxide metabolite (approximately 5 % of an oral dose after 12 hours). In most single-dose trials in HIV-1 infected subjects, or healthy subjects with serum sampling for 24 hours after dosing, the observed mean elimination half-life ($t_{½}$) ranged from 5 to 7 hours. In HIV-1–infected subjects, total clearance was 398.5 ± 69.1 mL/min (mean ± SD).

Tenofovir disoproxil
Following oral administration of a single 245 mg dose of tenofovir disoproxil to HIV-1-infected subjects in the fasted state, C_{max} was achieved in one hour. C_{max} and AUC values were 0.30 ± 0.09 micrograms per mL and 2.29 ± 0.69 µg•hr per mL, respectively. The oral bioavailability of tenofovir from tenofovir disoproxil in fasted subjects is approximately 25 %. Less than 0.7 % of tenofovir binds to human plasma proteins *in vitro* over the range of 0.01 to 25 micrograms per mL. Approximately 70-80 % of the intravenous dose of tenofovir is recovered as unchanged medicinal product in the urine within 72 hours of dosing. Tenofovir is eliminated by a combination of glomerular filtration and active tubular secretion with a renal clearance in adults with CrCl greater than 80 mL per minute of 243.5 ± 33.3 mL per minute (mean ± SD). Following oral administration, the terminal half-life of tenofovir is approximately 12 to 18 hours. *In vitro* studies have determined that neither tenofovir disoproxil nor tenofovir are substrates for the CYP450 enzymes.

Renal impairment

Doravirine
Renal excretion of doravirine is minor. In a study comparing 8 subjects with severe renal impairment to 8 subjects without renal impairment, the single dose exposure of doravirine was 31 % higher in subjects with severe renal impairment. In a population pharmacokinetic analysis, which included subjects with CrCl between 17 and 317 mL/min, renal function did not have a clinically relevant effect on doravirine pharmacokinetics. No dose adjustment is required in patients with mild, moderate or severe renal impairment. Doravirine has not been studied in patients with end-stage renal disease or in patients undergoing dialysis (see section 4.2).

Lamivudine
Studies with lamivudine show that plasma concentrations (AUC) are increased in patients with renal dysfunction due to decreased clearance. Based on the lamivudine data, Delstrigo is not recommended for patients with CrCl of < 50 mL/min.

Tenofovir disoproxil
Pharmacokinetic parameters of tenofovir were determined following administration of a single dose of tenofovir disoproxil 245 mg to 40 non-HIV infected adult subjects with varying degrees of renal impairment defined according to baseline CrCl (normal renal function when CrCl > 80 mL/min; mild

with CrCl = 50-79 mL/min; moderate with CrCl = 30-49 mL/min and severe with CrCl = 10-29 mL/min). Compared with subjects with normal renal function, the mean (% CV) tenofovir exposure increased from 2,185 (12 %) ng•h/mL in subjects with CrCl > 80 mL/min to respectively 3,064 (30 %) ng•h/mL, 6,009 (42 %) ng•h/mL and 15,985 (45 %) ng•h/mL in subjects with mild, moderate, and severe renal impairment.

The pharmacokinetics of tenofovir in non-haemodialysis adult subjects with CrCl < 10 mL/min and in subjects with end-stage renal disease managed by peritoneal or other forms of dialysis have not been studied.

Hepatic impairment

Doravirine
Doravirine is primarily metabolised and eliminated by the liver. There was no clinically relevant difference in the pharmacokinetics of doravirine in a study comparing 8 subjects with moderate hepatic impairment (classified as Child-Pugh score B primarily due to increased encephalopathy and ascites scores) to 8 subjects without hepatic impairment. No dose adjustment is required in patients with mild or moderate hepatic impairment. Doravirine has not been studied in subjects with severe hepatic impairment (Child-Pugh score C) (see section 4.2).

Lamivudine
The pharmacokinetic properties of lamivudine have been determined in subjects with moderate to severe hepatic impairment. Pharmacokinetic parameters were not altered by diminishing hepatic function. Safety and efficacy of lamivudine have not been established in the presence of decompensated liver disease.

Tenofovir disoproxil
The pharmacokinetics of tenofovir following a 245 mg dose of tenofovir disoproxil have been studied in non-HIV infected subjects with moderate to severe hepatic impairment. No clinically relevant differences in tenofovir pharmacokinetics were observed between subjects with hepatic impairment and unimpaired subjects.

Paediatric population

Mean doravirine exposures were similar in 54 paediatric patients aged 12 to less than 18 years and weighing at least 35 kg who received doravirine or doravirine/lamivudine/tenofovir disoproxil IMPAACT 2014 (Protocol 027) relative to adults following administration of doravirine or doravirine/lamivudine/tenofovir disoproxil. Exposures of lamivudine and tenofovir in paediatric subjects following the administration of doravirine/lamivudine/tenofovir disoproxil were similar to those in adults following administration of lamivudine and tenofovir disoproxil (Table 6).

Table 6: Steady state pharmacokinetics for doravirine, lamivudine, and tenofovir following administration of doravirine or doravirine/lamivudine/tenofovir disoproxil in HIV infected paediatric patients aged 12 to less than 18 years and weighing at least 35 kg

Parameter*	Doravirine†	Lamivudine‡	Tenofovir‡
AUC_{0-24} (µg•h/mL)	16.4 (24)	11.3 (28)	2.55 (14)
C_{max} (µg/mL)	1.03 (16)	2.1 (24)	0.293 (37)
C_{24} (µg/mL)	0.379 (42)	0.0663 (55)	0.0502 (9)

*Presented as geometric mean (%CV: geometric coefficient of variation)
†From population PK analysis (n=54)
‡From intensive PK analysis (n=10)
Abbreviations: AUC=area under the time concentration curve; C_{max}=maximum concentration; C_{24}=concentration at 24 hours

Elderly

Although a limited number of subjects aged 65 years and over has been included (n = 36), no clinically relevant differences in the pharmacokinetics of doravirine have been identified in subjects at least 65 years of age compared to subjects less than 65 years of age in a Phase 1 trial or in a population pharmacokinetic analysis. The pharmacokinetics of lamivudine and tenofovir have not been studied in subjects older than 65 years. No dose adjustment is required.

Gender

No clinically relevant pharmacokinetic differences have been identified between men and women for doravirine, lamivudine, and tenofovir.

Race

Doravirine
No clinically relevant racial differences in the pharmacokinetics of doravirine have been identified based on a population pharmacokinetic analysis of doravirine in healthy and HIV-1-infected subjects.

Lamivudine
There are no significant or clinically relevant racial differences in pharmacokinetics of lamivudine.

Tenofovir disoproxil
There were insufficient numbers from racial and ethnic groups other than Caucasian to adequately determine potential pharmacokinetic differences among these populations following the administration of tenofovir disoproxil.

5.3 Preclinical safety data

Reproductive toxicity

Doravirine
Reproduction studies with orally administered doravirine have been performed in rats and rabbits at exposures approximately 9 times (rats) and 8 times (rabbits) the exposure in humans at the recommended human dose (RHD) with no effects on embryo-foetal (rats and rabbits) or pre/postnatal (rats) development. Studies in pregnant rats and rabbits showed that doravirine is transferred to the foetus through the placenta, with foetal plasma concentrations of up to 40 % (rabbits) and 52 % (rats) that of maternal concentrations observed on gestation Day 20.

Doravirine was excreted into the milk of lactating rats following oral administration, with milk concentrations approximately 1.5 times that of maternal plasma concentrations.

Lamivudine
Lamivudine was not teratogenic in animal studies but there were indications of an increase in early embryonic deaths in rabbits at relatively low systemic exposures, comparable to those achieved in humans. A similar effect was not seen in rats even at very high systemic exposure.

Tenofovir disoproxil
Reproductive toxicity studies in rats and rabbits showed no effects on mating, fertility, pregnancy or foetal parameters. However, tenofovir disoproxil reduced the viability index and weight of pups in a peri-postnatal toxicity study at maternally toxic doses.

Carcinogenesis

Doravirine
Long-term oral carcinogenicity studies of doravirine in mice and rats showed no evidence of carcinogenic potential at estimated exposures up to 6 times (mice) and 7 times (rats) the human exposures at the RHD.

Lamivudine
Long-term carcinogenicity studies with lamivudine in mice and rats showed no evidence of carcinogenic potential at exposures up to 12 times (mice) and 57 times (rats) the human exposures at the RHD.

Tenofovir disoproxil
Oral carcinogenicity studies in rats and mice only revealed a low incidence of duodenal tumours at an extremely high-dose in mice. These tumours are unlikely to be of relevance to humans.

Mutagenesis

Doravirine
Doravirine was not genotoxic in a battery of *in vitro* or *in vivo* assays.

Lamivudine
Lamivudine was mutagenic in an L5178Y mouse lymphoma assay and clastogenic in a cytogenetic assay using cultured human lymphocytes. Lamivudine was not mutagenic in a microbial mutagenicity assay, in an *in vitro* cell transformation assay, in a rat micronucleus test, in a rat bone marrow cytogenetic assay, and in an assay for unscheduled DNA synthesis in rat liver.

Tenofovir disoproxil
Tenofovir disoproxil was mutagenic in the *in vitro* mouse lymphoma assay and negative in an *in vitro* bacterial mutagenicity test (Ames test). In an *in vivo* mouse micronucleus assay, tenofovir disoproxil was negative when administered to male mice.

Impairment of fertility

Doravirine
There were no effects on fertility, mating performance or early embryonic development when doravirine was administered to rats at up to 7 times the exposure in humans at the RHD.

Lamivudine
Lamivudine did not affect male or female fertility in rats.

Tenofovir disoproxil
Reproductive toxicity studies in rats and rabbits showed no effects on mating, fertility, pregnancy or foetal parameters.

Repeat dose toxicity

Doravirine
Administration of doravirine in animal toxicity studies was not associated with toxicity.

Lamivudine
Administration of lamivudine in animal toxicity studies at high doses was not associated with any major organ toxicity. At the highest dosage levels, minor effects on indicators of liver and kidney function were seen together with occasional reductions in liver weight. The clinically relevant effects

noted were a reduction in red blood cell count and neutropenia.

Tenofovir disoproxil
Findings in repeat-dose toxicity studies in rats, dogs and monkeys at exposure levels greater than or equal to clinical exposure levels and with possible relevance to clinical use included kidney and bone changes and a decrease in serum phosphate concentration. Bone toxicity was diagnosed as osteomalacia (monkeys) and reduced bone mineral density (BMD) (rats and dogs). The bone toxicity in young adult rats and dogs occurred at exposures ≥ 5-fold the exposure in paediatric or adult patients; bone toxicity occurred in juvenile infected monkeys at very high exposures following subcutaneous dosing (≥ 40-fold the exposure in patients). Findings in the rat and monkey studies indicated that there was a substance related decrease in intestinal absorption of phosphate with potential secondary reduction in BMD.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core

Croscarmellose sodium (E468)
Hypromellose acetate succinate
Magnesium stearate (E470b)
Microcrystalline cellulose (E460)
Silica, colloidal anhydrous (E551)
Sodium stearyl fumarate

Film-coating

Carnauba wax (E903)
Hypromellose (E464)
Iron oxide yellow (E172)
Lactose monohydrate
Titanium dioxide (E171)
Triacetin (E1518)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

30 months

6.4 Special precautions for storage

Store in the original bottle and keep the bottle tightly closed to protect from moisture. Do not remove the desiccant. This medicinal product does not require any special temperature storage conditions.

6.5 Nature and contents of container

Each carton contains a high-density polyethylene (HDPE) bottle with a polypropylene child-resistant closure with silica gel desiccants.

The following pack sizes are available:
- 1 bottle with 30 film-coated tablets
- 90 film-coated tablets (3 bottles of 30 film-coated tablets)

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Merck Sharp & Dohme B.V.
Waarderweg 39
2031 BN Haarlem
The Netherlands

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/18/1333/001
EU/1/18/1333/002

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 22 November 2018
Date of latest renewal: 23 June 2023

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency https://www.ema.europa.eu

ANNEX II

A. MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

A. MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer(s) responsible for batch release

Merck Sharp & Dohme B.V.
Waarderweg 39
2031 BN Haarlem
NETHERLANDS

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic safety update reports (PSURs)**

The requirements for submission of PSURs for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk management plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

Outer carton

1. NAME OF THE MEDICINAL PRODUCT

Delstrigo 100 mg / 300 mg / 245 mg film-coated tablets
doravirine/lamivudine/tenofovir disoproxil

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains100 mg of doravirine; 300 mg of lamivudine and 245 mg of tenofovir disoproxil.

3. LIST OF EXCIPIENTS

Contains lactose.
See package leaflet for further information

4. PHARMACEUTICAL FORM AND CONTENTS

Film-coated tablets
30 film-coated tablets
90 (3 bottles of 30) film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use. Swallow whole.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Keep the bottle tightly closed in order to protect from moisture.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Merck Sharp & Dohme B.V.
Waarderweg 39
2031 BN Haarlem
The Netherlands

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/18/1333/001
EU/1/18/1333/002 90 (3 x 30) tablets

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Delstrigo

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING

Bottle label

1. NAME OF THE MEDICINAL PRODUCT

Delstrigo 100 mg / 300 mg / 245 mg film-coated tablets
doravirine/lamivudine/tenofovir disoproxil

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains 100 mg of doravirine, 300 mg of lamivudine and 245 mg of tenofovir disoproxil.

3. LIST OF EXCIPIENTS

Contains lactose.
See package leaflet for further information

4. PHARMACEUTICAL FORM AND CONTENTS

30 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use.
Swallow whole.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Keep the bottle tightly closed in order to protect from moisture.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Merck Sharp & Dohme B.V.

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/18/1333/001
EU/1/18/1333/002 90 (3 x 30) tablets

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

17. UNIQUE IDENTIFIER – 2D BARCODE

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

B. PACKAGE LEAFLET

Package leaflet: Information for the user

Delstrigo 100 mg/300 mg/245 mg film-coated tablets
doravirine/ lamivudine/ tenofovir disoproxil

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist, or nurse.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor, pharmacist, or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Delstrigo is and what it is used for

What Delstrigo is
Delstrigo is used to treat HIV ('human immunodeficiency virus') infection. It belongs to a group of medicines called 'antiretroviral medicines'.

Delstrigo contains the active substances:
- Doravirine - a non-nucleoside reverse transcriptase inhibitor (NNRTI)
- Lamivudine - a nucleoside analogue reverse transcriptase inhibitor (NRTI)
- Tenofovir disoproxil - a nucleoside analogue reverse transcriptase inhibitor (NRTI)

What Delstrigo is used for
Delstrigo is used to treat HIV infection in adults, and adolescents aged 12 years and older weighing at least 35 kg. HIV is the virus that causes AIDS ('acquired immune deficiency syndrome'). You should not take Delstrigo if your doctor has told you that the virus causing your infection is resistant to any of the medicines in Delstrigo.

How Delstrigo works
Delstrigo works by preventing HIV from making more viruses in your body. This will help by:
- reducing the amount of HIV in your blood (this is called your 'viral load')
- increasing the number of white blood cells called '$CD4^+$ T'. This can make your immune system stronger. This may reduce your risk of early death or catching infections because your immune system is weak.

2. What you need to know before you take Delstrigo

Do not take Delstrigo
- if you are allergic to doravirine, lamivudine or tenofovir disoproxil or any of the other ingredients of this medicine listed in section 6.
- if you are taking any of the following medicines:
  - carbamazepine, oxcarbazepine, phenobarbital, phenytoin (medicines for seizure)

- rifampicin, rifapentine (medicines for tuberculosis)
- St. John's wort (*Hypericum perforatum*, a herbal remedy used for depression and anxiety) or products that contain it
- mitotane (a medicine to treat cancer)
- enzalutamide (a medicine to treat prostate cancer)
- lumacaftor (a medicine to treat cystic fibrosis)

Do not take Delstrigo if the above applies to you. If you are not sure, talk to your doctor, pharmacist, or nurse before taking Delstrigo. See also the list in section "Other Medicines and Delstrigo".

Warnings and precautions
Talk to your doctor, pharmacist, or nurse before taking Delstrigo.

Severe skin reactions
Severe skin reactions, including Stevens-Johnson syndrome/toxic epidermal necrolysis, have been reported in association with Delstrigo treatment. Stop using Delstrigo and seek medical attention immediately if you notice any of the symptoms related to these serious skin reactions described in section 4.

Worsening of hepatitis B infection
If you have both HIV and hepatitis B virus infections, your hepatitis B may get worse if you stop taking Delstrigo. You may require blood tests for several months after stopping treatment. Discuss your hepatitis B therapy with your doctor.

New or worsening kidney problems, including kidney failure
This can happen in some people who take Delstrigo. Your doctor will do blood tests to check your kidney function before and during treatment with Delstrigo.

Bone problems
This can happen in some people who take Delstrigo. Tell your doctor if you suffer from osteoporosis, have a history of bone fracture or if you have problems with your bones. Bone problems (manifesting as persistent or worsening bone pain and sometimes resulting in fractures) may also occur due to damage to kidney tubule cells (see section 4, Possible side effects). Tell your doctor if you have bone pain or fractures.

Tenofovir disoproxil may also cause loss of bone mass. The most pronounced bone loss was seen in clinical studies when patients were treated with tenofovir disoproxil in combination with a boosted protease inhibitor.

Overall, the effects of tenofovir disoproxil on long-term bone health and future fracture risk in adult and paediatric patients are uncertain.

Immune reactivation syndrome
This can happen when you start taking any HIV medicine, including Delstrigo. Your immune system may get stronger and begin to fight infections that have been hidden in your body for a long time. Tell your doctor right away if you start having any new symptoms after starting your HIV medicine.

Autoimmune disorders (a condition that occurs when the immune system attacks healthy body tissue) may also occur after you start taking medicines for the treatment of your HIV infection. Autoimmune disorders may occur many months after the start of treatment. If you notice any symptoms of infection or other symptoms such as muscle weakness, weakness beginning in the hands and feet and moving up towards the trunk of the body, palpitations, tremor or hyperactivity, please inform your doctor immediately to seek necessary treatment.

Children and adolescents
Do not give this medicine to children aged less than 12 years or weighing less than 35 kg. The use

of Delstrigo in children aged less than 12 years or weighing less than 35 kg has not yet been studied.

Other medicines and Delstrigo
Tell your doctor, pharmacist, or nurse if you are taking, have recently taken, or might take any other medicines. This is because other medicines may affect how Delstrigo works, and Delstrigo might affect the way some other medicines work.

There are some medicines you must not take with Delstrigo. See list under "Do not take Delstrigo" section.

Talk to your doctor before taking the following medicines with Delstrigo as your doctor may need to change the dose of your medicines:
- bosentan (a medicine to treat lung disease)
- dabrafenib (a medicine to treat skin cancer)
- lesinurad (a medicine to treat gout)
- modafinil (a medicine to treat excessive sleepiness)
- nafcillin (a medicine to treat some bacterial infections)
- rifabutin (a medicine to treat some bacterial infections such as tuberculosis)
- telotristat ethyl (a medicine to treat diarrhoea in people with carcinoid syndrome)
- thioridazine (a medicine to treat psychiatric conditions such as schizophrenia)

If your doctor decides you should take these medicines with Delstrigo, your doctor will prescribe a 100 mg tablet of doravirine to be taken daily, approximately 12 hours after your dose of Delstrigo.

Your doctor may check your blood levels or monitor for side effects if you take the following medicines with Delstrigo:
- ledipasvir/sofosbuvir (medicines used to treat hepatitis C infection)
- sirolimus (a medicine used to control your body's immune response after a transplant)
- sofosbuvir/velpatasvir (medicines used to treat hepatitis C infection)
- tacrolimus (a medicine used to control your body's immune response after a transplant)
- medicines (usually liquids) containing sorbitol and other sugar alcohols (such as xylitol, mannitol, lactitol or maltitol), if taken regularly

Pregnancy and breast-feeding
If you are pregnant or breastfeeding, think you may be pregnant, or are planning to have a baby, talk to your doctor about the risks and benefits of taking Delstrigo. It is preferable to avoid the use of Delstrigo during pregnancy. This is because it has not been studied in pregnancy and it is not known if Delstrigo will harm your baby while you are pregnant.

Breast-feeding is not recommended in women living with HIV because HIV infection can be passed on to the baby in breast milk.

If you are breast-feeding, or thinking about breast-feeding, you should discuss it with your doctor as soon as possible.

Driving and using machines
Use caution when driving, riding a bicycle, or operating machines if you feel tired, dizzy, or sleepy after taking this medicine.

Delstrigo tablets contains lactose
If you have been told by your doctor that you have an intolerance to lactose, talk to your doctor before taking this medicine.

3. How to take Delstrigo

Always take this medicine exactly as your doctor, pharmacist, or nurse has told you. Check with your doctor, pharmacist, or nurse if you are not sure. Delstrigo is a complete regimen taken as a single tablet for the treatment of HIV infection.

How much to take
The recommended dose is 1 tablet once a day. If you take certain medicines, your doctor may need to change the amount of doravirine you take. See "Other medicines and Delstrigo" section for a list of medicines.

Taking this medicine
- Swallow the tablet whole (do not crush or chew).
- This medicine can be taken with food or between meals.

If you take more Delstrigo than you should
Do not take more than the recommended dose. If you accidentally take more, contact your doctor.

If you forget to take Delstrigo
- It is important that you do not miss or skip doses of Delstrigo.
- If you forget a dose, take it as soon as you remember. But if your next dose is due within 12 hours, skip the dose you missed and take the next one at the usual time. Then continue your treatment as before.
- Do not take two doses of Delstrigo at the same time to make up for a missed dose.
- If you are not sure what to do, call your doctor or pharmacist.

If you stop taking Delstrigo
Do not run out of Delstrigo. Refill your prescription or talk to your doctor before your Delstrigo is all gone.

If you stop taking Delstrigo, your doctor will need to check your health often and do blood tests regularly for several months to check your HIV infection. If you have HIV infection and hepatitis B infection, it is especially important not to stop your Delstrigo treatment without talking to your doctor first. Some patients have had blood tests or symptoms indicating that their hepatitis has worsened after stopping lamivudine or tenofovir disoproxil (two of the three active substances of Delstrigo). If Delstrigo is stopped your doctor may recommend that you resume hepatitis B treatment. You may need blood tests to check how your liver is working for 4 months after stopping treatment. In some patients with advanced liver disease or cirrhosis, stopping treatment is not recommended as this may lead to worsening of your hepatitis, which may be life-threatening.

If you have any further questions on the use of this medicine, ask your doctor, pharmacist or nurse.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them. Do not stop taking this medicine without first talking to your doctor.

Stop using Delstrigo and seek medical attention immediately if you notice any of the following symptoms: reddish non-elevated, target-like or circular patches on the trunk, often with central blisters, skin peeling, ulcers of mouth, throat, nose, genitals and eyes. These serious skin rashes can be preceded by fever and flu-like symptoms (Stevens-Johnson syndrome/toxic epidermal necrolysis). The frequency of these reactions cannot be estimated from the available data.

Other side effects that may occur

Common: may affect up to 1 in 10 people:
- abnormal dreams, difficulty in sleeping (insomnia)
- headache, dizziness, sleepiness
- cough, nasal symptoms
- feeling sick (nausea), diarrhoea, stomach pain, vomiting, wind (flatulence)
- hair loss, rash
- muscle symptoms (pain, stiffness)
- loss of bone mass
- feeling tired, fever

Blood tests may also show:
- increased levels in liver enzymes (ALT)

Uncommon: may affect up to 1 in 100 people:
- nightmares, depression, anxiety, irritability, confusion, suicidal thoughts
- trouble concentrating, memory problems, tingling of hands and feet, stiff muscles, poor quality of sleep
- high blood pressure
- constipation, stomach discomfort, swollen or bloated stomach (abdominal distension), indigestion, soft stools, stomach spasms, frequent bowel movements, inflammation of the pancreas (pancreatitis) (causing stomach pain, vomiting)
- itchiness
- joint pain, breakdown of muscle tissue, muscular weakness
- feeling weak, general feeling of being unwell

Blood tests may also show:
- decreased number of white blood cells in your blood (neutropenia)
- decreased number of red blood cells in your blood (anaemia)
- decreased levels of platelets in your blood (you may bleed more easily)
- decreased levels phosphate
- decreased levels of potassium in your blood
- increased levels of creatinine in your blood
- increased levels in liver enzymes (AST)
- increased levels of lipase
- increased levels of amylase
- decreased levels of haemoglobin

The muscle pain, muscle weakness and decreases in potassium or phosphate in the blood may occur due to damage to kidney tubule cells.

Rare: may affect up to 1 in 1 000 people:
- aggression, hallucinations, difficulty adjusting to changes, mood changes, sleepwalking
- difficulty breathing, enlarged tonsils
- feeling of incomplete defecation
- enlarged liver or fatty liver, yellow skin or eyes, pain in the belly (abdomen) caused by inflammation of the liver
- inflammation of the skin due to allergy, redness on the cheeks, nose, chin or forehead, bumps or pimples on the face, swelling of the face, lips, tongue or throat
- muscle weakness, weakening of the bones (with bone pain and sometimes resulting in fractures)
- kidney damage, kidney stones, kidney failure, damage to kidney tubule cells, kidney injury, passing a lot of urine and feeling thirsty
- pain in the chest, feeling cold, pain, thirst

Blood tests may also show:
- decreased levels of magnesium
- lactic acidosis (excess lactic acid in the blood)
- increased levels of creatine phosphokinase

Very rare: may affect up to 1 in 10 000 people:
Blood tests may also show:
- failure of the bone marrow to produce new red blood cells (pure red cell aplasia)

Reporting of side effects
If you get any side effects, talk to your doctor, pharmacist, or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects, you can help provide more information on the safety of this medicine.

5. How to store Delstrigo

- Keep this medicine out of the sight and reach of children.
- Do not use this medicine after the expiry date which is stated on the bottle after EXP.
- The bottle contains desiccant protecting the tablets from moisture. There may be more than one in the bottle. Keep desiccant inside the bottle and do not throw away until you have finished taking all of the medicine.
- Keep the bottle tightly closed in order to protect from moisture.
- This medicinal product does not require any special temperature storage conditions.
- Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Delstrigo contains
- The active substances are 100 mg of doravirine, 300 mg of lamivudine and 245 mg of tenofovir disoproxil (as fumarate)
- The other ingredients are croscarmellose sodium E468; hypromellose acetate succinate; magnesium stearate E470b; microcrystalline cellulose E460; silica, colloidal anhydrous E551; sodium stearyl fumarate. The tablets are film-coated with a coating material containing the following ingredients: carnauba wax E903, hypromellose E464; iron oxide yellow E172; lactose monohydrate; titanium dioxide E171; and triacetin E1518.

What Delstrigo looks like and contents of the pack
Delstrigo is available as a yellow, oval-shaped, film-coated tablet, and is debossed with the corporate logo and 776 on one side and plain on the other side.

The following pack sizes are available:
- 1 bottle with 30 film-coated tablets
- 90 film-coated tablets (3 bottles of 30 film-coated tablets)

Not all pack sizes may be available in your country.

Marketing Authorisation Holder and Manufacturer
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For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

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Other sources of information

Detailed information on this medicine is available on the European Medicines Agency web site: https://www.ema.europa.eu.